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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,020	07/23/2001	Judith Zyskind	FLITRA.001DV1	4741

20995 7590 01/17/2003

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EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 01/17/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/912,020	Applicant(s) ZYSKIND ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3-5 7-9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 11/6/02, as Paper No. 12. Claims 1, 4, 6, 7, 11, 13 and 14 have been amended. New claims 18-20 have been added. Claims 1-20 are pending in the application and addressed herein.

Election/Restrictions

Applicant's election with traverse of SEQ ID NO: 325 in Paper No. 12 is acknowledged. The traversal is on the ground(s) that the claims have been amended such that they are all drawn to the polypeptide of SEQ ID NO: 325, the corresponding nucleic acid (SEQ ID NO: 165) which encodes said polypeptide, and two overlapping antisense nucleotides (SEQ ID NOS: 459 and 460) which significantly overlap (205 nucleotides overlap = ~70% overlap) and are inhibit the activity or reduce the amount of said polypeptide.

In response, it is noted that the prior Office Action indicated that an election of a single antisense molecule was required. In light of the amendment narrowing the claims to two specific antisense molecules which significantly overlap and are specific to a particular nucleic acid, both antisense molecules (SEQ ID NO 459 and 460) will be examined in the instant application. However, no other antisense molecules will be examined in future Actions (i.e. any additional sequences added in a future amendment will be withdrawn as non-elected by original presentation).

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. For example, see page 19lines 14 and 29. Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112, second paragraph

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Method claims require an active or positive step that accomplishes the goals for the method which were stated in the method's preamble. The instant claims lack such a step and are confusing because the additional method step(s) is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d1011, p.1011 (Bd. Pat. App. Int. 1986). The specific problem with the instant claims is that the steps presented are simply a method of inhibiting cellular proliferation. There is no requirement or active or positive step in the claims that cellular proliferation is actually accomplished. This is indefinite because it leaves the scope of the claim unclear as to whether it is required that the cellular proliferation is inhibited.

5. Claim 11-17 and 20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 recites the phrase, "a gene corresponding to one of SEQ ID NO: 165 or with activity against the product..." This phrase renders the claim indefinite because it appears that more than one gene (or SEQ ID NO.) is intended to be in the claim. Amending the claim to remove the phrase "one of" would obviate this rejection. Claims 12-17 and 20 are dependent claims and are rejected for the same reason.

Claim Rejections - 35 USC § 112, first paragraph

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims are drawn to a method of inhibiting proliferation of a cell by inhibiting the activity or reducing the amount of a specific polypeptide. The broadest claims are not limited to any particular method for inhibiting the activity or reducing the amount of the polypeptide (e.g., see claim 1), other claims encompass administering: 1) any compound to inhibit or reduce the polypeptide (e.g. see claim 4); 2) any antisense molecule (e.g. claim 5); 3)

any functional portion of antisense molecules SEQ ID NOS: 459 or 460 (e.g. claim 6); 4) at least 10 or more consecutive nucleotides of antisense molecules SEQ ID NOS: 459 or 460) (e.g. claim 7). Therefore, the claims encompass molecules for which there is no written description provided.

The Written Description Guidelines for examination of patent applications indicates, "the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or other chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show applicant was in possession of the claimed genus." (See MPEP 2100-164).

In the instant case, the broadest claims encompass administering any compound which inhibits the activity or reduced the amount of a polypeptide. Therefore these claims encompass a genus of millions of different compounds considering every compound which could inhibit the activity or reduce the level of the polypeptide. For instance the claim encompass drugs (such as small molecules or polypeptides) as well as antisense molecules that work directly or indirectly on the activity/level of the polypeptide. This large genus is represented in the specification by only the identification of two specific antisense molecules (SEQ ID NOS: 459-460). Regarding the claims that are drawn to functional portions of these molecules, it is noted that the written description guidelines indicate that functional characteristics coupled with known or disclosed correlation between structure and function is required. Here, there is no indication of any critical elements of the antisense molecules provided. Therefore, there is no indication which portions

of the antisense molecules would be functional portions and which portions would be non-functional portions. It is respectfully noted that a definition by function does not suffice to define the genus because it is only an indication of what the molecule does, rather than what it is. An amendment limiting the claims to the specifically antisense molecules of SEQ ID NO: 459 and 460 would obviate this rejection.

8. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for inhibiting the proliferation of E. coli, S. Typhimurium, E. cloacae or K. pneumoniae cells in vitro by administering an antisense nucleic acid sequence selected from the group consisting of SEQ ID NO: 459 and 460 to said cells wherein said administration of said antisense nucleic acid molecule results in inhibiting the proliferation of said cells;

does not reasonably provide enablement for the full breadth of the claim. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for inhibiting cellular proliferation by inhibiting the activity or reducing the level of the amino acid sequence of SEQ ID NO: 325. The specification indicates that the SEQ ID NO: 325 is a gene involved in proliferation E. coli and indicates that specific antisense molecules can be used to inhibit cellular proliferation of certain bacterial cells; thus it is asserted that the antisense molecules act as antibiotics. Therefore the nature of the Invention is antisense therapy.

The breadth of the claims

The broadest claims are very broad and encompass inhibiting cellular proliferation of any cell by administering any compound that inhibits the activity or reduces the level of the amino acid sequence of SEQ ID NO: 325. It is noted that the specification contemplates using the antisense molecules as antibiotics. Therefore the claims encompass inhibiting the proliferation of bacterial cells that are in an animal (i.e. in vivo) as well as inhibiting the proliferation of bacterial cells that are outside an animal (i.e. in vitro). As mentioned in the written description rejection above, the claims also encompass administering any compound comprising the antisense molecules and functional (i.e. proliferation-inhibiting fragments of the antisense molecules).

The unpredictability of the art and the state of the prior art

As mentioned above the claims encompass using the antisense molecules as antibiotics to inhibit the proliferation of bacterial cells in an animal. However, the relevant art recognizes

several problems with using antisense molecules for treatment in animals/humans. First, it is clear that ordinary, unmodified DNA and RNA oligonucleotides are rapidly degraded by enzymes in the body and that the resulting nucleoside monophosphates toxic (e.g. see Dove Nat. Biotech. 2002; 20:121-124; Lebedeva et al. Ann. Rev. Pharmacol. Toxicol. 2001; 41:403-419; and Branch TIBS 1998; 23:45-50). Furthermore, the art also recognizes that antisense molecules can have non-specific effects. Specifically, Branch teaches,

> "[T]he antisense field has been turned on its head by the discovery of 'non-antisense' effects, which occur when a nucleic acid drug acts on some molecule other than its intended target—often through entirely unexpected mechanism. Non-antisense effects are not necessarily bad. Indeed, some may prove to be a boon to the pharmaceutical industry because they offer an added source of potency. However, their unpredictability confounds research applications of nucleic acid reagents." (See p. 45 middle column).

Branch also indicates that antisense molecules that longer antisense molecules are not necessarily better and can have negative effects. Specifically, Branch teaches that increasing the length of the antisense molecule beyond the minimum is likely to decrease its specificity by stabilizing binding to mismatched sequences (see p. 47 last column). Figure 1 on page 48 of Branch indicates that a long antisense molecule may bind to the target RNA well as mismatched "by-stander" RNA and both RNAs get destroyed. Branch also teaches, "Because non-antisense effects are not currently predictable, rules for rational design cannot be applied to the production of non-antisense drugs. These effects must be explored on a case-by-case basis." (See p. 50, first column).

The "by-stander" effect also has to be considered when using the antisense molecules to inhibit the proliferation of other bacterial species. For example, it would be readily apparent to one of ordinary skill in the art there would likely be variations of the same gene in different species of bacteria. Therefore, it is possible that there could be mismatch binding of the

antisense molecules to other "by-stander" RNAs. Therefore one of ordinary skill in the art could not predictably use the antisense molecules of SEQ ID NO: 459 or 460 to inhibit the proliferation of any bacterial cell without performing additional experimentation.

Working Examples and Guidance in the Specification

The specification indicates that the specific antisense molecules of SEQ ID NO: 459 and 460 were given to E. coli, S. Typhimurium, E. cloacae or K. pneumoniae cells in vitro (i.e., not in an animal or a human) and the results indicate that the treatment inhibited proliferation of these cells (e.g., see Mol No. EcXA033 in the Table on p. 95, as well as the figures and Examples 1-3, p. 31-37).

However, the specification does not indicate that the antisense molecules were given to any animal having a bacterial infection. The specification doe not disclose that the antisense molecules were given to any other bacterial cells other than those already mentioned, nor does the specification indicate than any fragments of the antisense molecules have been tested or that any molecules comprising the antisense molecules of SEQ ID NO: 459 and 460 have been administered.

Quantity of Experimentation

Considering the breadth of the claims and the limited amount of working examples/guidance in the specification; additional experimentation would be required in order for one of ordinary skill in the art to: 1) identify all of the compounds encompassed by the claims (see written description rejection, above); 2) show that the compounds have an antiproliferative

effect on all of the cells encompassed by the claims in vitro; 3) test the efficacy of the compounds on animals that were infected with the bacterial cells.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the unpredictability of antisense therapy recognized in the art—especially the non-specific effects of antisense therapy, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed invention is undue.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
January 13, 2003

DAVE T. NGUYEN
PRIMARY EXAMINER